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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/534,130	12/30/2005	Ian Hector Frazer	21415-0015	8451

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EXAMINER	
EPPS FORD, JANET L	

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1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/534,130	FRAZER, IAN HECTOR	
	Examiner	Art Unit	
	Janet L. Epps-Ford	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *39-76* is/are pending in the application.

4a) Of the above claim(s) *66-70 and 72-76* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39-65 and 71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12-20-05; 2-05-07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 39-65 and 71, in the reply filed on 11/21/2007 is acknowledged. The traversal is on the ground(s) that the teachings of Frazer et al. do not read on the claimed invention because the polypeptides of Frazer et al. are expressed in cells and confer a particular phenotype, however the polynucleotides of the claimed invention are not expressed. This is not found persuasive because the instant claims do not recite that the synthetic polynucleotide is not expressed in the cells. On the contrary, the instant claims recite wherein the codon optimized polynucleotide is expressed however it produces a phenotype that is other than a phenotype conferred upon a cell by a polynucleotide that is expressed in the cell and that encodes the polypeptide. There is nothing in the claims that would suggest that the parent polynucleotide is not expressed in the cells. Applicant's arguments are therefore unpersuasive, and the claims remain restricted for the reasons of record.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 66-70, and 72-76 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 11-21-07.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 39-65 and 71 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5. Claim 39, last three lines recites the following: "[w]herein the **selected phenotype** is **other than a phenotype** conferred upon a cell by **a polynucleotide** that is expressed in the cell and that encodes the polypeptide." This phrase is vague and indefinite since it is unclear if the selected phenotype set forth in this phrase is the same selected phenotype recited in lines 2-4 of this claim which recites wherein the **selected phenotype** is "of a **different quality** than that conferred by a parent polynucleotide that encodes the same polypeptide." Furthermore, the nature of the "selected phenotype" is ambiguous to the extent that the ordinary skilled artisan would not be able to ascertain the scope of the claimed invention since there are two distinct definitions given for the selected phenotype, namely wherein the selected phenotype is of a different quality than that produced by the parent polynucleotide that produces the same polypeptide, and secondly wherein the selected phenotype is other than a phenotype conferred by a cell by a polynucleotide that is expressed in the cell that encodes the polypeptide. Claims 40-65 and 71, which depend from claim 39 are also rejected for the reasons set forth above.

6. Claims 41-43 recite the limitation "reporter gene" in claim 39. There is insufficient antecedent basis for this limitation in the claim.

7. Claim 54 recites the limitation "the tandem repeat of each of the synthetic constructs" in claim 39. There is insufficient antecedent basis for this limitation in the claim.

8. Claim 56 recites "[A] method according to claim 17," claim 17 was cancelled by Applicants; therefore the scope of this claim cannot be determined since it is unclear what method Applicants are referring to.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 39-65 and 71 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. (Written Description).

11. The instant claims are to a method for constructing a synthetic polynucleotide, and synthetic polynucleotides, wherein said method for constructing requires prior knowledge of the differences in phenotypic preferences of synonymous codons in a given polynucleotide as expressed in a given test organism. Moreover, the claims are drawn to a broad genus of "selected phenotypes," that are produced as the result of changing at least one codon of a parent polynucleotide to produce a synthetic

polynucleotide which encodes the same polypeptide, wherein the selected phenotype is different from that which is produced by the parent polynucleotide.

12. Although it is within the level of skill and knowledge of the ordinary skilled artisan to replace a given codon with a synonymous codon due to the degeneracy of the genetic code, it is not within the level of skill of the ordinary artisan to be able to predict which synonymous codons are preferably introduced into a parent polynucleotide that would produce a phenotype that is different from that produced by the parent polynucleotide, and further wherein said different phenotype is "*a selected phenotype*." Instant claims 44-48 recite wherein the selected phenotype is selected from: immunity, antigen tolerance, angiogenesis, anti-angiogenesis, amelioration of clinical symptoms, reduced or increased cell death, reduced or increased cell differentiation, reduced or increased cell proliferation, tumor or cancer regression, growth and repair of tissue or organ, decreased fibrosis, inhibition or reversal of cell senescence, increased or reduced cell migration, differential expression of protein between different cells or tissues of an organism or part thereof, trauma recovery, recovery from burns, antibiotic resistance or sensitivity, herbicide tolerance or sensitivity, starch biosynthesis or modification, fatty acid biosynthesis, disease resistance or tolerance, pest resistance or tolerance including insect resistance or tolerance, viral resistance or tolerance, fungal resistance or tolerance, a metabolic trait including sucrose metabolism, frost resistance or tolerance, stress tolerance, and improved food content or increased yields.

13. Moreover, without further experimentation the skilled artisan would not be able to predict which synonymous codons exhibit a difference in phenotypic preference in

comparison to a first codon in a parent polynucleotide in a test organism or part thereof. The scope of the test organism in the instant claims encompasses wherein the test organism is a unicellular, or multi-cellular organism, including wherein said multi-cellular organism is an animal, mammal or plant.

14. To the extent that there is no direct correlation between the structure of full scope of synthetic (i.e. codon optimized) polynucleotides encompassed by the instant claims and the full scope of "selected phenotypes" encompassed by the instant claims, it is clear that *de novo* experimentation would have to be performed in order to identify those particular preferred codons within a given polynucleotide that are necessary to produce the plurality of selected phenotypes encompassed by the instant claims. According to the Guidelines for Examination of Patent Applications Under the 35 USC 112 ¶ 1, "Written Description" Requirement, see January 5, 2001 (Vol. 66, No. 4, pages 1099-1111) Federal Register: "[T]o satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the

invention was complete, or by describing distinguishing identifying characteristics sufficient to show that applicant was in possession of the claimed invention."

15. The person of ordinary skill in the art would not recognize the common attributes or features possessed by the members of the genus of synthetic polynucleotides encompassed by the instant claims, wherein the synthetic polynucleotides comprise specific synonymous codons having a differential preferred phenotype in comparison to the parent polynucleotide which produces the same polypeptide.

16. In the instant case, due to the necessity for further experimentation in order to identify the full scope of synonymous codons necessary to produce a phenotype different from that normally associated with a parent polynucleotide, it is therefore concluded that Applicants were not in possession of the full scope of the claimed invention as of the filing date of the instant application.

17. Claims 39-65 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.

As stated above, the instant claims are to a method for constructing a synthetic polynucleotide, wherein said method for constructing requires prior knowledge of the differences in phenotypic preferences of synonymous codons in a given polynucleotide as expressed in a given test organism. Moreover, the claims are drawn to a broad genus of "selected phenotypes," that are produced as the result of changing at least one codon of a parent polynucleotide to produce a synthetic polynucleotide which encodes the same polypeptide, wherein the selected phenotype is different from that which is produced by the parent polynucleotide. Moreover, instant claims 44-48 recite wherein the selected phenotype is selected from: immunity, antigen tolerance, angiogenesis, anti-angiogenesis, amelioration of clinical symptoms, reduced or increased cell death,

reduced or increased cell differentiation, reduced or increased cell proliferation, tumor or cancer regression, growth and repair of tissue or organ, decreased fibrosis, inhibition or reversal of cell senescence, increased or reduced cell migration, differential expression of protein between different cells or tissues of an organism or part thereof, trauma recovery, recovery from burns, antibiotic resistance or sensitivity, herbicide tolerance or sensitivity, starch biosynthesis or modification, fatty acid biosynthesis, disease resistance or tolerance, pest resistance or tolerance including insect resistance or tolerance, viral resistance or tolerance, fungal resistance or tolerance, a metabolic trait including sucrose metabolism, frost resistance or tolerance, stress tolerance, and improved food content or increased yields.

18. Moreover, the scope of the test organism in the instant claims encompasses wherein the test organism is a unicellular, or multi-cellular organism, including wherein said multi-cellular organism is an animal, mammal or plant.

Although it is clear that the prior art, for example Zolotukhin et al. teach how to make a synthetic polynucleotide construct having had codons replaced with synonymous codons that exhibit higher translational efficiency in mammalian cells than those comprising wild-type codons, there is no specific guidance given in the specification as filed for preparing specific synthetic polynucleotides having a differential phenotypic preference in comparison to wild-type polynucleotides, and further wherein the differential phenotypic preference is among the plurality of selected phenotypes listed above.

The specification as filed teaches the use of constructs of the general format: Eukaryotic promoter-ATG-(XXX)6-Gene of Interest-polyadenylation signal in the various examples, wherein (XXX)6 refers to 6 copies of each of the possible synonymous codon triplets that code for an amino acid. It is clear that optimal codons can be identified using these constructs, such that the translational efficiency of a given sequence is optimized. However, it is not clear that merely identifying these sequences having optimized translational efficiency would necessarily result in the identification of those synthetic polynucleotides which confer the plurality of selected phenotypes, not associated with the parent polynucleotide, when expressed in the plurality of unicellular and multicellular organisms encompassed by the instant claims. Moreover, it is evident that in each example a total of 59 gene constructs were constructed, however each gene constructed had to be tested in order to identify their ability to produce a differential phenotype that *was related to the phenotype associated* with the parent polynucleotide. There is no guidance for producing an entirely distinct phenotype from a synthetic polynucleotide produced by introducing synonymous codons into a parent polynucleotide.

As stated above, although it is within the level of ordinary skill in the art to design a nucleic acid construct comprising synonymous codons, however it is not possible to identify which codon replacements result in a desired phenotype without further unpredictable experimentation.

Applicant's disclosure of Examples 1-4 does not provide the skilled artisan with sufficient guidance for practicing the full scope of the claimed invention without need for undue experimentation.

Claim Rejections - 35 USC § 102

19. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

20. Claims 39 and 71 are rejected under 35 U.S.C. 102(b) as being anticipated by Frazer et al. WO 9902694A1.

21. A synthetic nucleic acid sequence and a method are disclosed for selectively expressing a protein in a target cell or tissue of a mammal. Selective expression is effected by replacing at least one existing codon of a parent nucleic acid sequence encoding a protein of interest with a synonymous codon to produce a synthetic nucleic acid sequence having altered translational kinetics compared to the parent nucleic acid sequence. The synonymous codon is selected such that it corresponds to an iso-tRNA which, when compared to an iso-tRNA corresponding to the at least one existing codon, is in higher abundance in the target cell or tissue relative to one or more other cells or tissues of the mammal, see pages 73-74. This disclosure anticipates instant claim 71.

22. Claims 39, 44, 49-50, 52-53, and 71 are rejected under 35 U.S.C. 102(b) as being anticipated by Zolotukhin et al. {Zolotukhin et al. (1996) J. Virology. 70:4646-4654}.

23. Zolotukhin et al. provides guidance on making a genetically modified mammal, specifically a guinea pig, by introducing a synthetic polynucleotide into the eye of the guinea pig, wherein said synthetic polynucleotide had had codons replaced with synonymous codons that exhibit a higher translational efficiency in a mammalian cell then a polynucleotide comprising the wild type codons (Abstract, pg. 4646, Materials and Methods). Zolotukhin et al. teaches designing a humanized GFP by replacing synonymous codons in GFP with human codons (pg. 4649, col. 1) Zolotukhin et al. states that differences in the populations of isoaccepter tRNAs in different cells leads to poor translation efficiency (pg. 4648, col. 1).

24. Further, Zolotukhin et al. identified specific Leu, Ser, and Val jellyfish GFP codons for replacement with synonymous human codons (pg. 4649, col. 1). Zolotukhin et al. then modified 88 codons in a jellyfish GFP nucleic acid sequence to produce a synthetic humanized GFP construct. Zolotukhin et al. then transfected 293 cells with constructs comprising the wild-type sequences and those containing the humanized GFP sequences. The humanized sequence consistently produced 5 to 10 times more cells scored as positive for GFP than the jellyfish sequence (pg. 4649, col. 2). Zolotukhin et al. also virally infected 293 cells with the plasmids packaged in viral vectors, which separately comprising the humanized GFP and jellyfish sequences. Zolotukhin et al. observed "no detectable GFP expression" from the jellyfish GFP infected cells, while 70% of the humanized GFP infected cells were positive for GFP expression (pg. 4650, col. 1). The advantage of viral infection over standard plasmid transfection methods, is that with viral infection typically only one copy of a plasmid is

introduced into each cell. This gives the practitioner a clearer picture of how the sequence is being expressed in a cell, without any masking effects due to multiple plasmids transfecting the same cell.

25. Claims 39-40, 44, 49-55, and 71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seed et al. (28 March 1996, WO 96/09378), in view of Rosenberg et al. (1993, J. Bacteriol., 175:716-722).

26. Seed et al. teaches a method of replacing low usage codons with synonymous high usage codons. The high usage codons have a higher rate of translation compared to the low usage codons. Seed et al. replaced low usage codons in HIV-1 gpl20 with high usage human codons (p 10, lines 19-27), which allowed a high level of synthetic gp 120 expression in human cervical carcinoma cells (HeLA cells) and human kidney carcinoma cells (293T). Prior to transfection of cells in vitro, the synthetic gp 120 polynucleotide was linked to a regulatory and inserted into a vector. The tests were also performed using monkey undifferentiated epithelial cells (cos-7 cells) and monkey kidney carcinoma cells (CV1). A precursor cell is any cell in which a particular wild type protein is not expressed. A differentiated cell is a cell in which a synthetic protein, corresponding to a particular wild type protein, is expressed at a higher level than the wild type protein. The synonymous codons to be used were determined by comparing frequency of codon usage of highly expressed human genes with that of the env gene (table 1 p9-10). An inherent property of low usage or rare codons is a low abundance of the corresponding iso-tRNA. Seed et al. discloses that translational efficiencies of the synthetic polypeptide can range from 110% to 10,000% of the wild-type polypeptide (pg.

2 lines 12-13). Seed et al. discloses that synonymous codons can be codons which are used at a high frequency by the genes of the mammal from which the target cell is derived or alternatively high frequency, synonymous codons can be selected from a group of different origin than the target cells (pg. 24, lines 27-29). Seed et al. list preferred or synonymous codons on page 1 lines 27-30 that include: tgc (Cys), ggc (Gly), ccc (Pro), acc (Thr), and aag (Lys). Seed et al. also discloses that the synthetic genes are useful for methods of gene therapy (page 41, last sentence). Seed et al. does not expressly disclose a method of measuring codon translation efficiency using a tandem repeat of codons linked to a reporter gene.

27. Seed et al. does not disclose a measurement of iso-tRNA abundance in cells. Rosenberg et al. supplements the guidance provided by Seed et al., by teaching a method of testing the translational efficiency of individual codons comprising: linking a tandem repeat of a particular codon to a reporter gene, transforming E. coli with the same construct, and comparing the level of reporter protein produced in conjunction with a particular codon against the level of reporter protein produced in conjunction with a synonymous codon, as a measurement of translational efficiency (pg. 717, col. 2 lines 1-7). In particular a tandem repeat of high usage cgu (Arg) codons substantially increased translation of test mRNAs as compared to controls (pg. 720, lines 3-6). The synthetic polynucleotides are linked to a regulatory polynucleotide and inserted into a vector prior to introduction into E.coli. Rosenberg et al. disclose that "frequencies of use of synonymous codons reflect the relative abundance of corresponding tRNA that recognize them."

28. Based on the guidance provided by Seed et al., on a teaches a method of replacing low usage codons with synonymous high usage codons, for use in gene therapy, the guidance of Rosenberg et al. on identifying the translational efficiency of individual codons, it would have been prima facie obvious to the person of ordinary skill in the art at the time the invention was made to combine the teachings of Seed et al., and Rosenberg et al. to produce a synthetic DNA construct, wherein the codons have been replaced with synonymous codons that exhibit a higher translational efficiency in mammalian cells. A practitioner in the art would have been motivated to combine the teachings of Seed et al., and Rosenberg et al. to make a synthetic DNA construct, wherein the codons have been replaced with synonymous codons that exhibit a higher translational efficiency in mammalian cells.

29. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 10:00 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Janet L. Epps-Ford/
Primary Examiner, Art Unit 1633